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Ultrasound and biochemical findings in intrauterine growth retardation

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The early recognition of fetal maldevelopment due to chronic placental insufficiency is of decisive importance if perinatal mortality and morbidity are to be further reduced. This can be achieved by direct and **indirect methods**, i.e. cephalometry and thoracometry using ultrasound on the one hand, and **biochemical tests** of the function of the feto-placental unit, on the other. **Estriol, pregnandiol** and **HPL levels** and some **placental enzymes** are here of special interest. In this investigation an attempt was made to asses the diagnostic value of the various parameters and to suggest when they should be used.

Curriculum vitae

Jürg KUNZ, *born 1942, Zurich, Studied medicine at University of Zurich, 1962–69. Then 2 years surgery with prof.* M. SCHAMAUN. *Then training in obstetrics and gynecology at the University Womens clinic, Zurich (prof.* W. E. SCHREINER*). Main interests: Perinatology, particularly monitoring of mother and child during pregnancy and delivery.*

1 Material and method

A total of 83 patients presently, or with a case history of risk hospitalised because of suspect placental insufficiency, was investigated. Twin pregnancies and those with doubtful duration were excluded. In the third trimester of pregnancy the following determinations were made: An average of 4 determinations of the **biparietal head diameter** using the B-scan method (Vidoson), 10 determinations of **estriol** and 3 of **pregnandiol in urine** [13, 50] and 6 **HPL determinations** in the serum [49], 7 determinations of **heat stable alkaline phosphatase (HSAP)** [9], all per individual case. Biparietal head diameter values were transferred to a standard curve that was in agreement with the one reported by HOLLÄNDER [42]. Growth retardation was assumed if the last two values showed the same trend with the date being certain and were below two standard deviations or showed decreased progress. Biochemical parameters were considered to be pathological if they were below 95% of the normal values, with two values being outside this normal range or with 3 or more values being continuously below the 95% normal range. Maturity was assessed after birth from neurological and somatic signs of maturity according to DUBOWITZ [25]. Infants were diagnosed as small for date if their birth weight was below the 10th percentile on the LUBCHENKO curve [62].

2 Results

Fifteen of the 83 newborn were small for dates. Five had a gestational age of less than 37 weeks, 4 in the 35/36 week and one in the 30.5 week. A further 11 prematures was in the group of 68 normotrophic children.

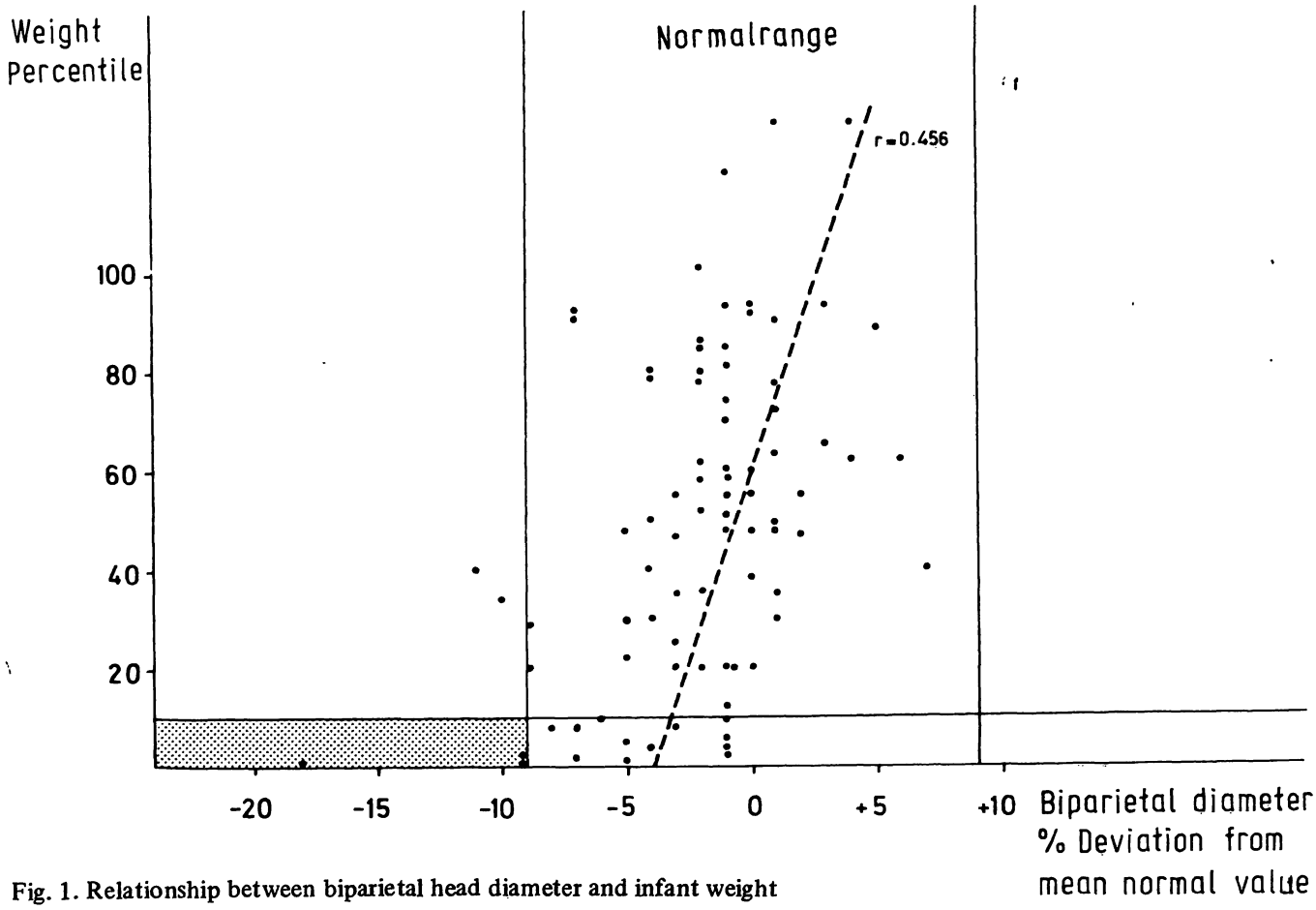

Fig. 1. Relationship between biparietal head diameter and infant weight

Fig. 1 shows that there is a good correlation between **biparietal head diameter** and body weight. However, only 3 out of the 15 small for date infants were below the lower limit of the norm. The remaining 81 (98%) were within normal limits, 71% below the curve for mean values. In twelve SGA infants the head diameter was normal prenatally and increased normally.

Fig. 2 shows a very good correlation between weight percentile and the percentage deviation from the normal mean of **estriol excretion**. In all SGA cases values were found to be decreased. Ten were outside the 95% normal limits and 5 were still at least 40% below those limits. In infants with body weights between the 10th and 50th percentile estriol values were below, the normal mean in 44%.

Weight percentiles and **HPL concentration** in maternal serum (Fig. 3) also correlated well. In 8 out of 15 SGA infants values were below the 95% normal range. In 7 cases HPL maternal values were above the mean. For normal infants reliability was 68% but in 19% there was a false positive finding. Inspite of a proper correlation **pregnandiol determinations** showed up only one of the SGA infants (Fig. 4).

In contrast to the three hormonal parameters there was no correlation between weight percentile and the percentage deviation of the **HSAP concentration** from the mean (Fig. 5). Five SGA values were below the 95% range and 9 below the mean value. Results are summarized in Tab. I.

Tab. I.

Weight of newborn	Number	Cephalometry	E_3	HPL	P_2	HSAP
10. Percentile	15	20%	67%	53%	7%	33%
10.–90. Percentile	68	98%	83%	68%	95%	86%

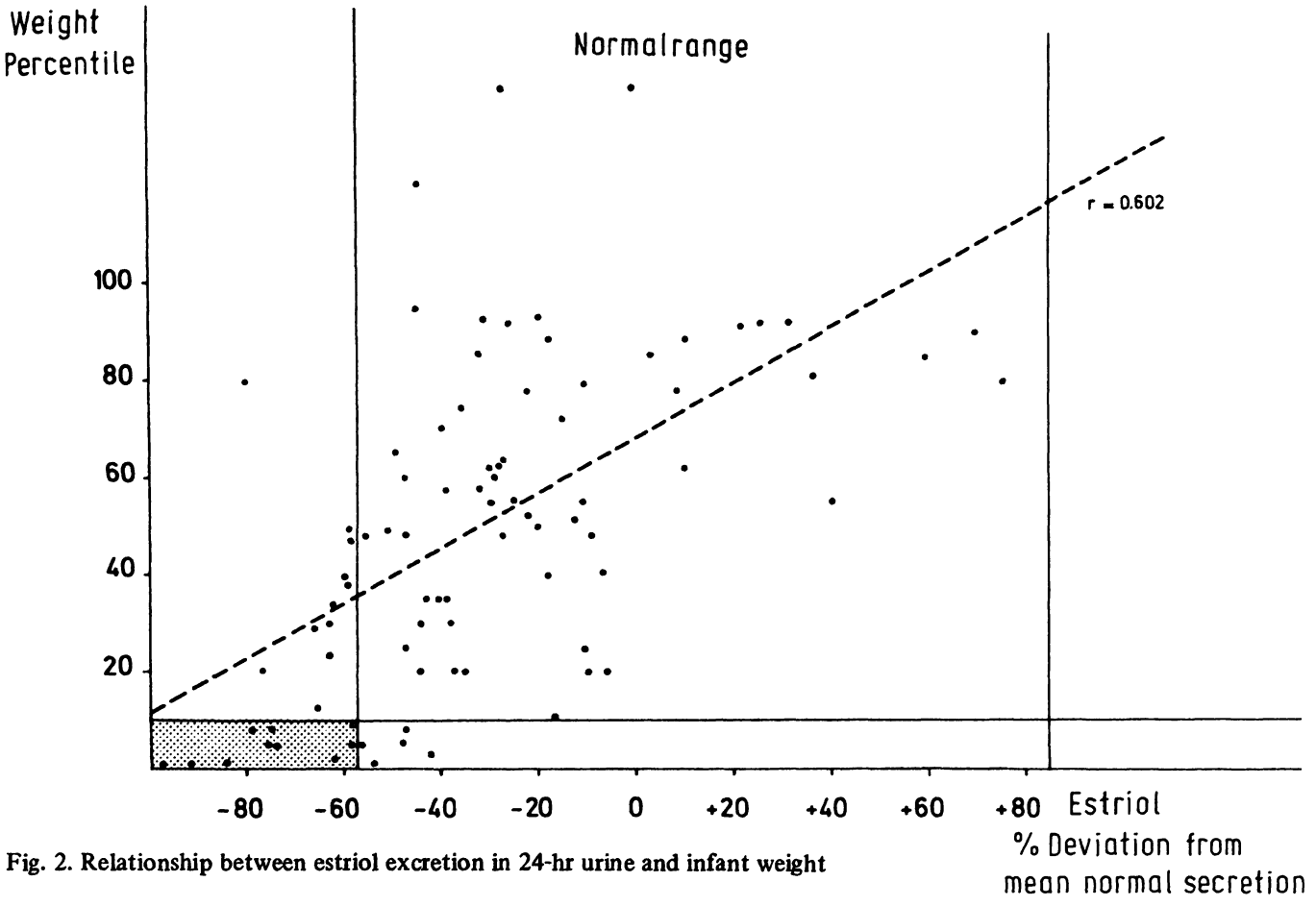

Fig. 2. Relationship between estriol excretion in 24-hr urine and infant weight

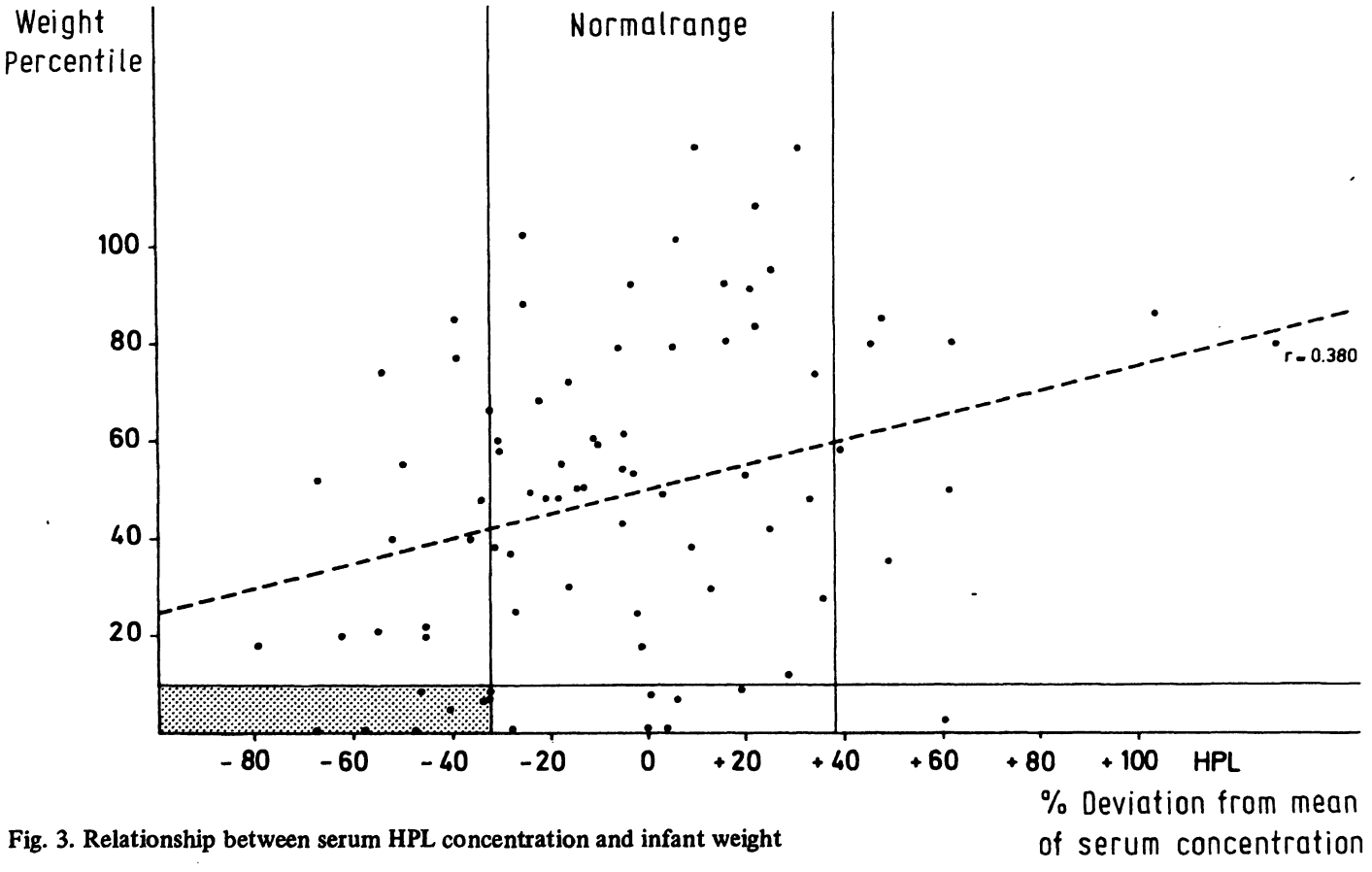

Fig. 3. Relationship between serum HPL concentration and infant weight

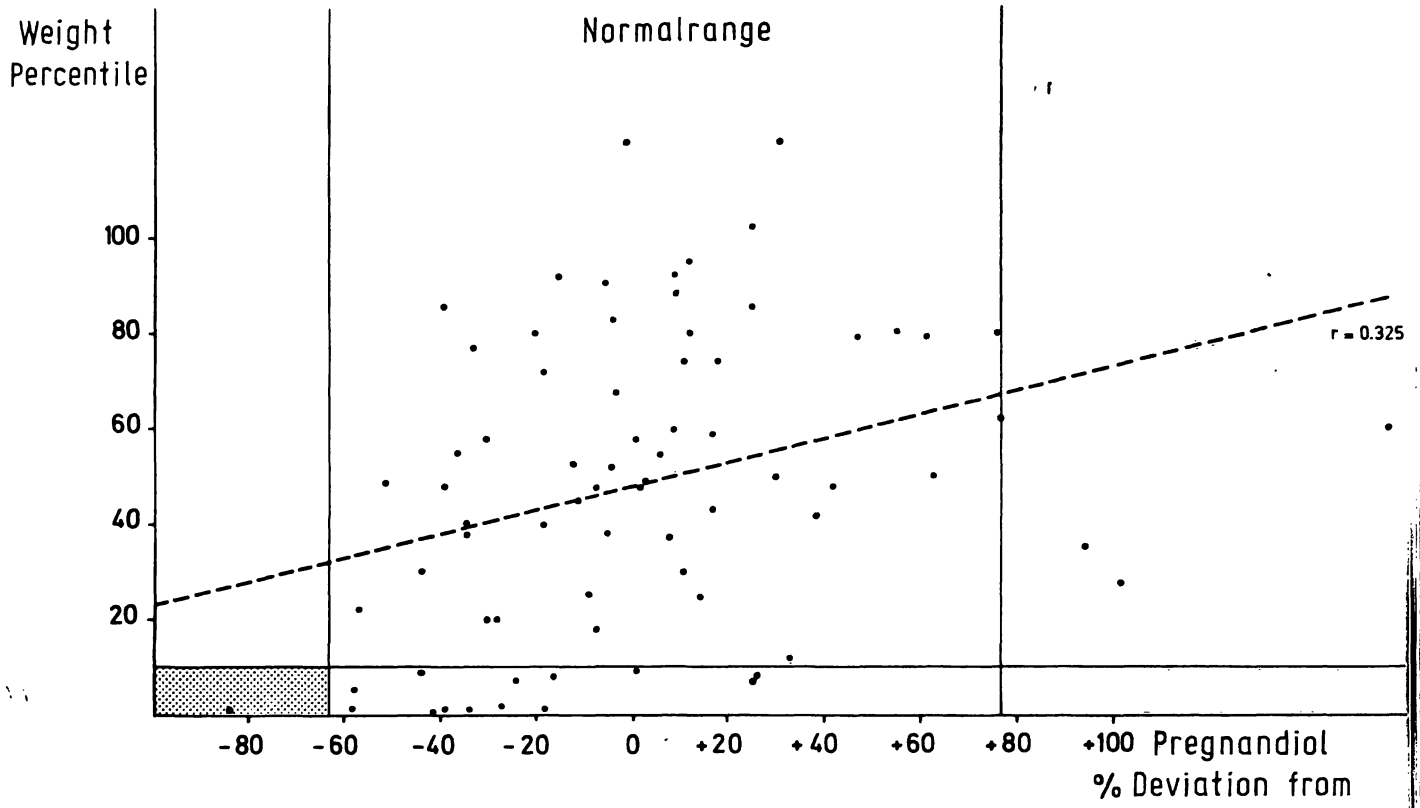

Fig. 4. Relationship between pregnandiol excretion in 24-hr urine and infant weight

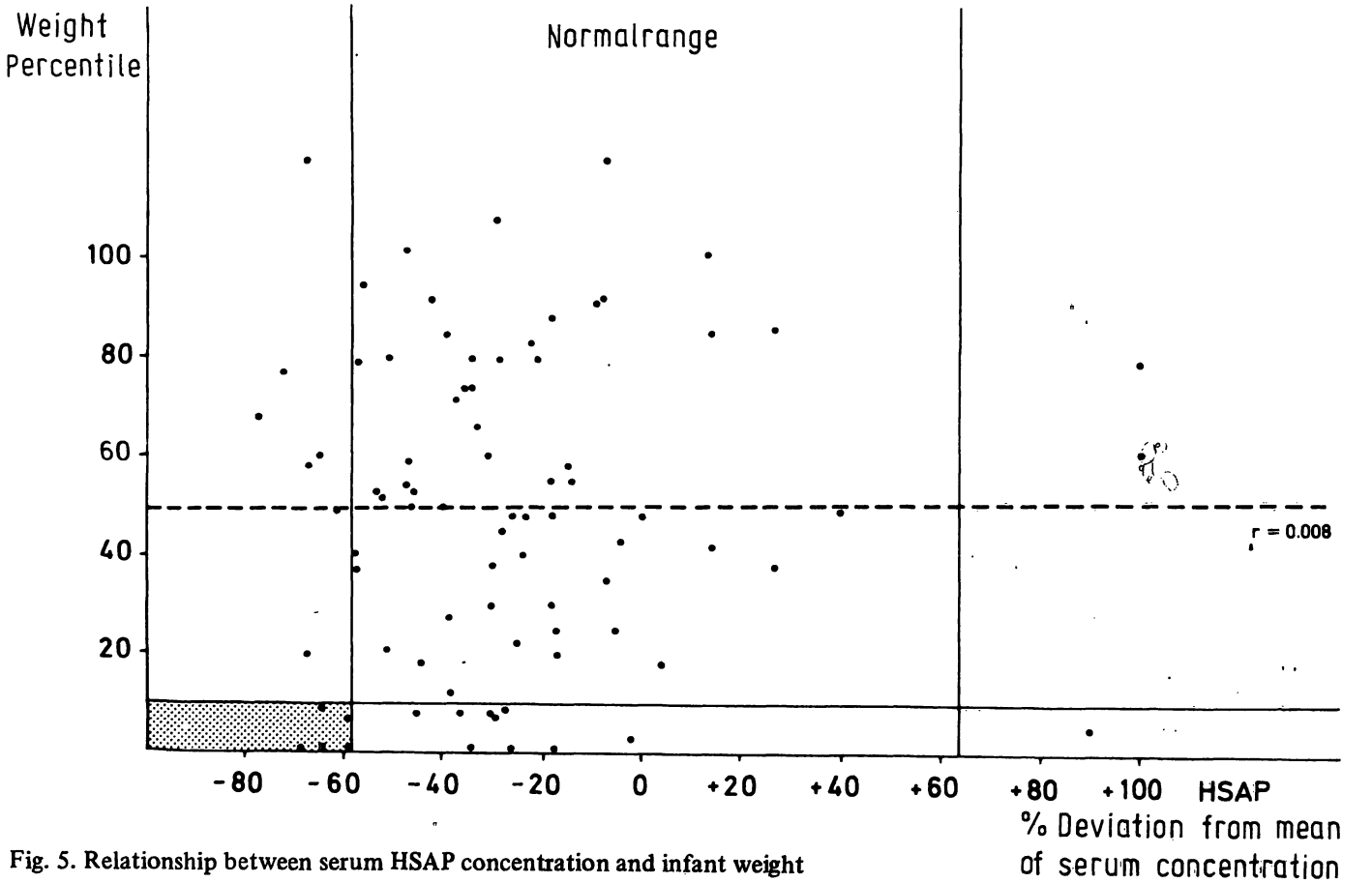

Fig. 5. Relationship between serum HSAP concentration and infant weight

3 Discussion

Cephalography gave a good correlation between body weight and biparietal diameter. Three of the 15 SGAs were diagnosed echographically. In 12 the diameter was normal and increased normally prenatally. The linear relationship between biparietal diameter and infant weight has been described [39, 70, 82]. HOLLÄNDER [43] diagnosed 45% of SGAs from the absolute diameter, HINSELMANN [42] could predict growth retardation from the 30th week of pregnancy onwards in 70% of cases. The **poor prognostic value of the diameter in our series** is not surprising, since chronic placental insufficiency which is expressed only in the last trimester affects brain and cranial growth only slightly and least of all organs [35, 36, 43]. This is in contrast to the effects of early impairment of fetal growth. Fetal retardation is better diagnosed from low weekly growth rates considered to be 0.16 cm [90] to 0.18 cm [86]. CAMPBELL [15] uses this to diagnose 68% of SGAs with 18% false positives. Similar data have been reported by others [15, 36, 41, 43, 55, 59, 90]. Fetal abdominal circumference or additional thoracometry [37] were reliable up to 75% and thus better than the head diameter. However reference points are required to make these reproducible. A diameter of 8.5 to 9.4 cm at term indicates a weight of more than 2500 g [11, 43, 54, 57, 58, 82, 86]. In addition several formulas for calculating birth weight from echographically determined values have been suggested [4, 39, 45, 53, 54, 58, 81, 86, 92]. Inspite of a reliability of 68 to 90% deviations in body weight between 300 to 500 g were found. All agree that **cephalometry can diagnose growth retardation only if at least three determinations are made at weekly intervals for 2 weeks.**

In contrast to a few others [34, 46, 51, 87] we found a **good correlation between body weight and estriol excretion** in 24-hr-urine. Ten out of our 15 SGAs were below the 95% range and 5 were 40% below the mean normal value. In most other reports 60 to 84% of SGA deliveries showed low estriol values with 19% false positive findings [1, 6, 7, 8, 10, 16, 18, 19, 21, 23, 24, 26, 28, 29, 30, 32, 33, 65, 68, 83, 88, 89, 91]. It must be mentioned that **low estriol values need not always indicate placental insufficiency and that normal values do not exclude such an insufficiency** [63].

This also explains the idea that growth retardation and low estriol values may be secondary consequences of abnormal fetal development [17, 34, 51, 87]. Thus low estriol values often accompanied deformities [7, 84], genetic aberrations [63, 88] and adrenal hypoplasia [29]. **For the EPH syndrome in the group at risk a very good correlation between body weight and estriol excretion was always found** [26, 91]. Perinatal mortality rises up to 45% as growth retardation is increased [10, 26, 63, 69]. Depending on the duration of pregnancy some define a danger zone of 5–12 mg estriol/24 hrs [1, 26, 32, 38, 48, 63, 88] or a value less than 25% of the mean [47]. **All agree that repeated tests must be made, since single values are of little value.** BOOG et al. [12] in contrast to us, conclude that cephalometry is a better diagnostic tool than estriol determinations for the diagnosis of intrauterine growth retardation.

Plasma estriol and estradiol levels are also decreased during fetal growth retardation [66, 20, 56].

There was a good correlation between **maternal plasma HPL** and infant weight and 8 of our 15 SGA infants showed HPL values below the 95% normal limit. This correlation and diagnostic reliability with respect to SGA has been confirmed [40, 64, 79, 80, 83, 85]. Others found a relation to placental weight [5, 73, 74] not confirmed by SCIARRA et al. [75].

The **great range of normal HPL levels in the last trimester** has often been considered to limit the value and clinical use of this test [77, 79]. In order to improve the diagnostic value and to underline placental function a limit of 7 μg/ml was set for underweight infants [64] and below 4 μg/ml for danger to the fetus [78, 85]. Perinatal mortality was 24% for hypertensive pregnancies and rose to 56% in severe cases.

Only one out of 15 SGA infants could be detected from **pregnandiol values**. This may be due to the wide range of values and may explain contradictory reports. The correlation was confirmed [1, 46, 47, 76, 91], suspected [71, 72] or rejected [21, 51, 52, 65]. In underweight children low [14, 16, 31, 72] or unchanged values [65] have been reported.

In contrast to previous work [2, 19] only values

below 95% of the normal were taken into consideration for **HSAP concentrations.** Five out of 15 SGAs could be detected although there was no correlation with body weight. Others also found no correlation [18, 19, 28]. Reliability is reported to vary from 13.8 to 77% [2, 3, 18, 19, 89]. A correlation with placental weight has also been reported [18]. Although supported by some [44, 67] **HSAP concentration is of little value as a screening test** [28, 89] even though **it may reflect a chronic placental insufficiency.**

Thus, according to our results **24-hour-urinary estriol and HPL levels in the serum are the most valuable parameters for diagnosing intrauterine growth retardation** due to chronic placental insufficiency. Hence serial determinations of estriol and HPL are recommended if the case history contains a death at delivery, dysmaturity, pregnancy complications such as hypertension, chronic renal disease, cardiac symptoms, diabetes mellitus, haemorrhages in the second half of pregnancy etc. and in patients whose uterus appears small for date.

Summary

An attempt was made to make an early diagnosis of intrauterine growth retardation due to chronic placental insufficiency using ultrasound cephalometry and biochemical tests of placental function.

We examined 83 hospitalised patients in whom there was a risk or suspicion of chronic placental insufficiency. For each patient an average of 4 determinations were made of **head diameter**, 10 of **estriol** and 3 of **pregnandiol urinary excretion**, 6 **serum HPL** and 7 of **heat stable alkaline phosphatase (HSAP).** Fetal growth retardation was assumed if the last 2 determined head diameters were below the normal curve with the same tendency and with term being well predicted. Biochemical parameters were considered to indicate pathological changes if they were 95% below normal values, with 2 below this range or 3 continuously falling below the normal level. Infants were assessed after birth both neurologically and somatically according to DUBOWITZ. Small for date infants were those whose birth weight was below the 10th percentile (LUBCHENKO). This was found to be the case in 15 out of 83 newborns five of whom were younger than 37 weeks.

These 15 could be diagnosed before birth with various degrees of certainty. For estriol and HPL this was 67% or 53% and these two parameters were found to be the most valuable. Cephalometry was found to be less valuable with 20%, pregnandiol levels with 9% and placental HSAP with 33%.

Hence it is recommended to perform serial determinations of estriol and HPL in the third trimester of pregnancy in all patients with histories indicative of fetal growth retardation and in those in whom the uterus appears small for date.

Keywords: Cephalometry, chronic placental insufficiency, estriol, pregnandiol, heat stable alkaline phosphatase, HPL, intrauterine growth retardation.

Zusammenfassung

Ultraschallbefunde und biochemische Parameter bei intrauteriner Mangelentwicklung

Mittels Ultraschall-Kephalometrie und Überprüfung der biochemischen Funktionen der fetoplazentaren Einheit wurde der Versuch unternommen, eine intrauterine fetale Wachstumsretardierung als Folge einer chronischen Plazentarinsuffizienz möglichst frühzeitig zu erkennen.

Die Untersuchung umfaßte 83 ausgewählte, hospitalisierte Patientinnen mit aktuellem oder anamnestischem Risiko und klinischem Verdacht auf eine chronische Plazentarinsuffizienz. Pro Fall lagen im dritten Schwangerschaftstrimenon durchschnittlich 4 Messungen des **biparietalen Kopfdurchmessers**, 10 Bestimmungen der **Östriol-** und 3 der **Pregnandiolausscheidung** im Urin, 6 **HPL-Werte (Human Placental Lactogen)** im Serum und 7 Messungen der **hitzestabilen alkalischen Phosphatase (HSAP)** vor. Lagen die zwei zuletzt gemessenen biparietalen Durchmesser bei gleichbleibender Tendenz und gesichertem Termin unterhalb der doppelten mittleren Abweichung der Normwertkurve oder fehlte eine regelrechte Progredienz wurde eine fetale Wachstumsretardierung angenommen. Bei den biochemischen Parametern wurden folgende Werte als pathologisch angesehen: Abfall unter den 95%-Normbereich, wobei 2 Werte des Abfalles außerhalb dieses Bereiches liegen mußten oder kontinuierlicher Verlauf von 3 oder mehr Werten unterhalb dem Normbereich. Die klinische Beurteilung der Kinder erfolgte postpartal anhand der neurologischen und somatischen Reifezeichen nach DUBOWITZ. Als Mangelgeburt wurden Neugeborene mit einem Geburtsgewicht unter der 10. Perzentile (LUBCHENKO) klassiert. Diese Bedingung erfüllten 15 von 83 Neugeborenen, wovon 5 ein Gestationsalter von weniger als 37 Wochen aufwiesen.

Die 15 intrauterinen Mangelentwicklungen konnten antepartal mittels den durchgeführten Serienmessungen mit unterschiedlicher Treffsicherheit erfaßt werden. Sie betrug für Östriol und HPL 67% bzw. 53%, womit diesen beiden Parametern am meisten Bedeutung zukommt. Als weniger zuverlässig erwiesen sich mit 20% Treffsicherheit die Kephalometrie, mit 9% die Pregnandiolbestimmung und mit 33% das plazentare Enzym HSAP.

Serienmessungen von Östriol und HPL sind demnach im dritten Schwangerschaftstrimenon bei allen Schwangeren mit belasteter Anamnese und bei Patientinnen, bei denen der Uterus "small for date" erscheint, empfehlenswert.

Schlüsselwörter: Chronische Placentarinsuffizienz, Hitzestabile alkalische Phosphatase, HPL, Intrauterine Mangelentwicklung, Kephalometrie, Östriol, Pregnandiol.

Résumé

Résultats ultrasoniques et biochimiques en cas de malnutrition intra-utérine

A l'aide de la céphalométrie ultrasonique et de l'analyse des fonctions biochimiques de l'unité foeto-placentaire, nous avons tenté de détecter au plus tôt un retard de croissance foetale intra-utérine consécutive à une insuffisance placentaire chronique.

L'examen a porté sur 83 parturientes hospitalisées et sélectionnées, présentant un risque actuel ou anamnésique ainsi que clinique d'insuffisance placentaire chronique. Pour chacun des cas, on a effectué jusqu'au troisième trimestre de grossesse en moyenne 4 mesurages du **diamètre crânial biparíétal**, 10 calculs d'**élimination d'oestriol** et 3 de **prégnandiol** dans l'urine, 6 **valeurs de HPL** (Human Placental Lactogen) dans le sérum et 7 calculs de **phosphatase alcaline thermostabile (HSAP)**. Dans les cas où les deux dernières mesures du diamètre biparíétal sont restés, pour une tendance stationnaire et un terme sûr, au-dessous de l'écart-type doublé des courbes normales et terme sûr, au-dessous de l'écart-type doublé des courbes normales et où manquait toute progression régulière, on a assumé que la cause en était dûe à un retardement de la crvissance foetale. Pout les paramètres biochimiques, on a considéré les valeurs suivantes comme étant pathologiques: Baisse de la courbe de croissance au-dessous de la zone normale de 95% à condition que deux des valeurs de baisse se situent en dehors de cette zone ou que la courbe continue de 3 ou plus de ces valeurs se maintienne au-dessous de la zone normale. L'examen clinique des enfants a été effectué post partum à l'appui des signes d'maturité neurologiques et somatiques d'après DUBOWITZ. On a placé dans la classification de naissance carentielle les nouveaux-nés ayant un poids à la naissance inférieur au 10. percentile (LUBCHENKO), ce qui fut le cas pour 15 des 83 nouveaux-nés dont 5 atteignirent un âge de gestation inférieur à 37 semaines.

Les 15 cas de carence intra-utérine avaient pu être observés ante partum avec une précision diversifiée par les séries de mesures effectuées: Cette précision a été respectivement de 67 et 53% pour l'oestriol et le HPL qui représentent donc les facteurs les plus importants. Par contre, la céphalométrie, la définition de prégnandiol et l'enzyme placentaire HSAP ont apporté un degré moindre d'exactitude qui n'a pas dépassé, respectivement, 20, 9 et 33%.

En conclusion, il est recommandé d'effectuer des séries de mesures d'oestriol et de HPL au 3ème trimestre de grossesse chez toutes les femmes enceintes ayant une anamnèse «chargée» ou chez lesquelles l'utérus semble petit pour la date de gestation.

Mots-clés: Céphalométrie, HPL, Insuffisance placentaire chronique, malnutrition intrautérine, oestriol, prégnandiol, phosphatase alcaline thermostabile.

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